UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/073,596	05/06/1998	RALPH M. STEINMAN	ARG010RC	9977

43852 7590 09/27/2012

Argos Therapeutics, Inc.
4233 TECHNOLOGY DRIVE
DURHAM, NC 27704

EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
09/27/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte RALPH M. STEINMAN, KAYO INABA,
and GEROLD SCHULER

Appeal 2011-006598
Application 09/073,596
Technology Center 1600

Before TONI R. SCHEINER, DONALD E. ADAMS, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 99, 101, 104-113, 116, 120, and 142-145, directed to a composition comprising mature dendritic cells expressing modified antigen.

The Examiner has rejected the claims on the grounds of anticipation, obviousness, lack of written descriptive support, and indefiniteness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claims 99, 101, 104-113, 116, 120, and 142-145 are pending and on appeal. Claims 1-98, 100, 102, 103, 114, 115, 117-119, and 121-141 have been canceled (App. Br. 3). Claims 101 and 120 are representative:

101. An *in vitro* composition comprising mature dendritic cells expressing modified antigen and derived from an *in vitro* culture of an enriched and expanded population of proliferating dendritic cell precursors by a method comprising:

providing a tissue source comprising dendritic cell precursors;

treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors;

treating the tissue source to obtain a population of cells suitable for culture *in vitro*;

culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain nonadherent cells and cell clusters;

subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors;

serially subculturing the cell aggregates one or more times to enrich the proportion of dendritic cell precursors; and

continuing to culture the dendritic cell precursors for a period of time to allow them to mature into mature dendritic cells;

culturing the dendritic cells *in vitro* in the presence of an antigen for a time sufficient to allow the antigen to bind to the dendritic cells, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.

120. An *in vitro* composition comprising mature dendritic cells expressing a modified antigen and derived from an *in vitro* culture of a population of proliferating dendritic cell precursor cells by a method comprising culturing dendritic cell precursor cells in a culture medium comprising GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors; serially subculturing the proliferating dendritic cell precursors at intervals which provide for the continued proliferation of said dendritic cell precursors; and exposing the cells to antigen *in vitro*, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.

The claims stand rejected as follows:

I. Claims 99, 101, 104-113, 116, 120, and 142-145 under 35 U.S.C. § 102(a) as anticipated by Pancholi.[1]

II. Claims 99, 101, 104-113, 116, 120, and 142-145 under 35 U.S.C. § 103(a) as unpatentable over Inaba,[2] Steinman,[3] and Markowicz.[4]

III. Claims 99, 101, 104-113, 116, 120, and 142-145 under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support (new matter).

IV. Claim 120 under 35 U.S.C. § 112, second paragraph, as indefinite.

DISCUSSION

I.

Claims 99, 101, 104-113, 116, 120, and 142-145 stand rejected as anticipated by Pancholi.

The present application is a continuation-in-part of U.S. Application No. 07/861,612, which was filed April 1, 1992.[5] Appellants contend that the

---

[1] P. Pancholi et al., *Dendritic cells efficiently immunoselect mycobacterial-reactive T cells in human blood, including clonable antigen-reactive precursors*, 76 IMMUNOLOGY 217-234 (1992).

[2] Kayo Inaba et al., *Dendritic Cells Pulsed with Protein Antigens In Vitro Can Prime Antigen-specific, MHC-restricted T cells In Situ*, 172 J. EXP. MED. 631-640 (1990).

[3] Ralph M. Steinman et al., *The Sensitization Phase of T-Cell-Mediated Immunity*, 546 ANNALS N.Y. ACADEMY OF SCIENCE 80-90 (1988).

[4] Serglusz Markowicz & Edgar G. Engleman, *Granulocyte-Macrophage Colony-stimulating Factor Promotes Differentiation and Survival of Human Peripheral Blood Dendritic Cells In Vitro*, 85 J. CLIN. INVEST. 955-961 (1990).

presently claimed invention is fully supported by the priority application, and therefore, Pancholi is not available as prior art as it was published in June 1992 (App. Br. 8).

The Examiner has denied "the benefit of priority" (Ans. 8) based on a finding that several steps recited in the claims are not disclosed in the priority application. Specifically, the Examiner finds that the '612 priority application does not disclose "'treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell [DC] precursors'" (Ans. 8); "the cells being cultured with an antigen as is recited in the last step of Claims 101 and 120" (*id.*); "'modified' antigens" (*id.*); or "allowing culture 'for a time sufficient to allow the antigen to bind to the dendritic cells and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells'" (*id.*).

In addition, the Examiner finds that "the modified antigens of the instant specification are disclosed only in the context of antigen-activated DCs. And in the instant context it appears that antigen-activation occurs before maturation (which requires additional culture after activation). Thus, antigen-activated DCs are not synonymous with mature DCs" (*id.* at 10). The Examiner finds that the priority application discloses "'antigen-activated' dendritic cells" (*id.* at 11), but does not disclose "that these are the mature dendritic cells of the instant claims" (*id.*). According to the Examiner, "[i]t appears that Appellant is attempting to subtly modify the claimed invention so that it fits modern immunological terms and encompass

---

[5] Appellants submitted a copy of U.S. Application No. 07/861,612 as Appendix B of their Appeal Brief.

concepts that were not known . . . when the parent applications were filed" (*id.* at 11).

If we understand the Examiner's position, it is that dendritic cells are now understood to undergo a maturation process that occurs upon and/or after antigen-activation, and that this post-activation maturation process is not described in the priority application - thus "mature" dendritic cells meant one thing in the art when the priority application was filed, and something else when the present application was filed.

Nevertheless, we agree with Appellants that all of the steps in the claims, in the order claimed, are fully described in the '612 priority application, as detailed in Appendix A of Appellants' Brief, even if they are not disclosed *in haec verba*. In addition, we note pages 7-9, 22, and 40 of the '612 priority application in particular. We agree with Appellants that both the present application and the priority application disclose that "antigen-activated dendritic cells (also referred to, *inter alia*, as dendritic cells expressing modified antigen) are dendritic cells that are prepared according to the methods of the invention and are further (*i.e.*, additionally) treated by exposure to antigen" (Reply Br. 5). That is, we agree that the antigen-activated dendritic cells referred to in the '612 priority application are cells that have previously been cultured in the presence of GM-CSF "for a period of time sufficient to allow them to mature into mature dendritic cells" (App. No. 07/861,612, p. 8, ll. 4-6). [6]

---

[6] *See e.g.*, page 22, lines 10-15 of the '612 priority application, which states: "The antigen-activated dendritic cells of the invention are produced by exposing antigen, in vitro, to the dendritic cells prepared according to the

We agree with Appellants that the present claims are entitled to the benefit of the filing date of U.S. Application 07/861,612, and therefore, Pancholi is not available as prior art.

Accordingly, the rejection of claims 99, 101, 104-113, 116, 120, and 142-145 as anticipated by Pancholi is reversed.

II.

Claims 99, 101, 104-113, 116, 120, and 142-145 stand rejected as unpatentable over Inaba, Steinman, and Markowicz. Claim 101 is representative.

The Examiner finds that Inaba "teaches mouse DCs [dendritic cells] cultured with antigen . . . that process and express the modified antigen" (Ans. 5), but "does not teach DCs matured in GM-CSF" (*id.*).

However, the Examiner finds that Steinman "teaches the enrichment and culturing of both mouse and human immature DCs found in blood, as well as bone marrow . . . and that, 'maturation is driven by factors such as IL-1 and GM-CSF'" (*id.*), and "that 'GM-CSF is critical in mobilizing active DCs at the onset of a cell-mediated immune response'" (*id.* at 5-6).

---

method of the invention." *See also*, page 8, lines 15-19 of the '612 priority application, which states: "Another embodiment of the invention are [sic] antigen-activated dendritic cells prepared according to the method of the invention which antigen-activated dendritic cells have been exposed to antigen and express modified antigen for presentation to and activation of T cells." The "method of the invention" referred to here is the method disclosed in the '612 priority application, by which dendritic cells undergo a degree of maturation in the presence of GM-CSF.

In addition, the Examiner finds that Markowicz teaches that GM-CSF profoundly affects the morphology and viability of dendritic cells isolated from peripheral blood, allowing them to survive up to six weeks in culture while still retaining their ability to stimulate the proliferation of T cells (*id.* at 6).

The Examiner concludes that it would have been obvious for one of ordinary skill in the art to add GM-CSF to cultured dendritic cells, such as those of Inaba or Steinman, given the teachings of Markowicz that GM-CSF profoundly affects the morphology and extends the viability of dendritic cells isolated from peripheral blood, and that the resultant cultures would be indistinguishable from those made according to the methods outlined in the Specification.

Appellants do not dispute the Examiner's findings with respect to the teachings of the individual references, but do contend that Markowicz "teaches away from the use of GM-CSF to induce proliferation" (App. Br. 10), in that Markowicz concludes that "'the number of viable cells as well as the number of branched cells per well **remained stable over time, suggesting that GM-CSF does not cause DC to divide and proliferate**'" (*id.* at 10-11). Appellants further contend that Steinman does not "teach or suggest that GM-CSF plays any role in stimulating cell proliferation" either (*id.* at 11). Moreover, Appellants contend that the "role of GM-CSF in maturation [as taught by Steinman] would not provide motivation for adding GM-CSF to a dendritic cell culture such as that of Inaba without some suggestion that those cells were immature, which is absent in the cited references" (Reply Br. 11).

Finally, Appellants contend that the Examiner's finding that adding GM-CSF to Inaba's cultured dendritic cells would result in "the GM-CSF-cultured DCs as claimed" (Ans. 6) is incorrect. Appellants contend that "simply adding GM-CSF to a dendritic cell culture such as that of Inaba's would not, without much more, result in the claimed invention" (Reply Br. 11).

These arguments are not persuasive. First, Appellants have not addressed the Examiner's conclusion that it would have been obvious to add GM-CSF to Inaba's cultures to extend their viability in culture, as taught by Markowicz, and therefore, have not adequately rebutted the Examiner's proferred reason for combining the references.

Second, there is no dispute that Inaba's cultures, without the addition of GM-CSF are different than the claimed cultures, but the relevant question is whether simply adding GM-CSF to Inaba's cultures would result in a composition objectively and demonstrably different from the composition resulting from the method steps outlined in the present claims. It may well be that Appellants are correct in asserting that adding GM-CSF to Inaba's cultures would not result in the claimed invention, However, Appellants are in a better position than the Examiner to provide objective evidence on this point, but have not done so on this record. Attorney argument is not evidence. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974).

On this record, we will affirm the rejection of claim 101 as unpatentable over the combined teachings of Inaba, Steinman, and Markowicz, as Appellants have not rebutted the Examiner's findings and conclusions with argument or evidence. Because they have not been

separately argued, claims 99, 104-113, 116, 120, and 142-145 fall together with claim 101. 37 C.F.R. § 41.37(c)(1)(iv).

III.

Claims 99, 101, 104-113, 116, 120, and 142-145 stand rejected under 35 U.S.C. § 112, first paragraph, written description, "for the introduction of new matter into the claims" (Ans. 7).

The Examiner finds that:

> The specification and claims as originally filed do not provide support for the invention as now claimed, specifically, a method step of allowing culture, "for a time sufficient to allow the antigen to bind to the dendritic cells and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells".

(*Id.*)

Nevertheless, we agree with Appellants that support can be found for this step, at the very least, in the present Specification at page 9, line 35 through page 10, line 4. Moreover, this step is disclosed in Example 2 of the '612 priority application (*see* page 40, lines 4-28 of the '612 priority application).

The rejection of claims 99, 101, 104-113, 116, 120, and 142-145 as lacking adequate written descriptive support in the Specification as filed is reversed.

IV.

Claim 120 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite. According to the Examiner, "it is unclear whether or not the actions of the claim are actually intended to be method steps. If so, then the

steps must be separated and indented as is required of all method steps" (Ans. 7-8).

We agree with Appellants that one of skill in the art would understand the bounds of the claim, and that the claim comports with the statute, "[i]n view of the explicit statement in the claim regarding the use of a method and the proper use of active verbs and punctuation" (Reply Br. 12). We agree with Appellants that "it is unclear . . . that a more vertical and differently spaced arrangement of the claim would have any effect on the meaning or construction of the claim" (*id.*).

The rejection of claim 120 as indefinite is reversed.

SUMMARY

I. The rejection of claims 99, 101, 104-113, 116, 120, and 142-145 as anticipated by Pancholi is reversed.

II. The rejection of claim 101 as unpatentable over Inaba, Steinman, and Markowicz is affirmed. Because they are not separately argued claims 99, 104-113, 116, 120, and 142-145 fall together with claim 101. 37 C.F.R. § 41.37(c)(1)(iv).

III. The rejection of claims 99, 101, 104-113, 116, 120, and 142-145 as lacking adequate written descriptive support is reversed.

IV. The rejection of claim 120 as indefinite is reversed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc